NAFLD: A PRIMARY CARE PERSPECTIVE

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DISCLOSURES

• No relevant conflicts-of-interest

• Discussion of off-label use: none
OVERVIEW

1. Terminology & natural history

2. Diagnosis of NAFLD in primary care

3. Treatment of NAFLD in primary care
OBJECTIVES

• Know the difference in natural history between NAFL and NASH

• Recognize and apply to your practice the biology-based thresholds for serum ALT

• Be familiar with the NASPGHAN recommendations for diagnosis and treatment of NAFLD in children
Terminology & Natural History
**TERMINOLOGY**

Nonalcoholic fatty liver disease (NAFLD)

Nonalcoholic fatty liver (NAFL)  Nonalcoholic steatohepatitis (NASH)
WHY DOES IT MATTER?
NAFLD IS HIGHLY PREVALENT

NAFLD is the most common chronic liver disease in children:

- 0.7% of 2-4 year olds
- 17.3% of 15-19 year olds
- 38% of obese children & adolescents

*Schwimmer et al, Pediatrics, 2006*
NAFLD IS ASSOCIATED WITH SIGNIFICANT MORBIDITY

- Among adults, NAFLD is the 2nd most common indication for liver transplantation*

- NAFLD is predicted to become the most common cause for liver transplantation within a decade

*Wong et al, Gastroenterology, 2015
Diagnosis of NAFLD
DIAGNOSTIC CHALLENGES IN NAFLD

• Highly prevalent condition
• Variable natural history
• Lack of biomarker to risk stratify
• No FDA-approved therapies
• Screening tools are imperfect
• Gold standard diagnostic test (liver biopsy) is costly and invasive
COMMON SCENARIOS IN PRIMARY CARE

• Active screening of asymptomatic, at-risk populations

• Incidental imaging findings suggestive of fatty liver
ACTIVE SCREENING

1. Expert Committee Recommendations for Prevention, Assessment, & Treatment of Overweight & Obesity, Barlow (2007)

2. NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of NAFLD in Children (2016)
1) EXPERT COMMITTEE RECOMMENDATIONS FOR PREVENTION, ASSESSMENT, & TREATMENT OF OVERWEIGHT & OBESITY, BARLOW (2007)

- Biennial screening, starting at age 10 years, for children:
  - with BMI ≥95th percentile (obese)
  - with BMI 85th-94th percentile (overweight), who have other risk factors

- ALT > 2X ULN should prompt consultation with a pediatric gastroenterologist/hepatologist
TWO IMPORTANT QUESTIONS...

1. What constitutes a risk factor to determine which overweight children to screen?

2. What is meant by 2X ULN for ALT?
RISK FACTORS FOR NAFLD

- T2DM
- Insulin resistance
- Dyslipidemia
- Elevated triglycerides
- Acanthosis nigricans
- Central adiposity
- Hypertension
- Obstructive Sleep Apnea
- Age ≥ 10 years
- Male gender
- Hispanic ethnicity
- Family history of NAFLD
WHAT IS MEANT BY 2X ULN FOR ALT?

Barlow’s paper uses 2X ULN and 60 U/L interchangeably...but the field has evolved!

SAFETY Study: Alanine Aminotransferase Cutoff Values Are Set Too High for Reliable Detection of Pediatric Chronic Liver Disease

_Gastroenterology, 2010_
Survey 43 free-standing children’s hospitals in US
Median ULN for ALT 52 U/L (range 30-90)
Only 44% of hospitals used gender-specific norms
95\textsuperscript{th} percentile for ALT (\textit{i.e.} the ULN) was:

- 26 U/L for boys
- 22 U/L for girls
HOW DID 43 CHILDREN’S HOSPITALS MISS IT?
2. NASPGHAN CLINICAL PRACTICE GUIDELINE FOR THE DIAGNOSIS AND TREATMENT OF NAFLD IN CHILDREN (2016)

• Screening with ALT for NAFLD is appropriate for all obese children, and for overweight children with additional risk factors, beginning at age 9-11 years.

• Interpretation of ALT should be based on biologically-derived upper limits of normal, and not individual laboratory ranges.

• Persistently (> 3 months) elevated ALT, more than 2X ULN, should be evaluated for NAFLD, and other causes of chronic hepatitis.
2. NASPGHAN CLINICAL PRACTICE GUIDELINE FOR THE DIAGNOSIS AND TREATMENT OF NAFLD IN CHILDREN

- ALT >80 U/L warrants increased clinical concern and timely evaluation, as the likelihood of significant liver disease is higher

- Routine ultrasound is **not recommended** as a screening test for NAFLD in children due to low sensitivity and specificity
LIMITATIONS OF STANDARD US-BASED SCREENING FOR FATTY LIVER

- Trans-abdominal US doesn’t do a good job of picking up liver fat when < 33%
  - fatty liver is defined as >5% steatosis

- PPV of US to detect steatosis: 47-62%*

- Poor concordance between grade of steatosis by US compared to histology or MRI

*Schwimmer, Hepatology, 2016
NAFLD SCREENING SUMMARY RECOMMENDATION

1. Obtain screening ALT between ages 9-11 yrs, if obese, or if overweight with RFs.

2. ALT < 52 for boys < 44 for girls consider re-screening in 2-3 years, absent new RFs.

3. ALT 52-80 for boys 44-80 for girls.
   - Counsel on healthy lifestyle habits & repeat ALT in 3-6 months.

4. ALT < 52 for boys < 44 for girls return to standard care.

5. ALT >52 for boys >44 for girls further testing, or referral.
   - Persistently elevated ALT, or other concerning liver panel result.
   - Further testing or referral.
   - ALT decreasing and other liver indices normal.
   - Follow using clinical judgement.

6. ALT >80 for boys/girls.
   - Counsel on healthy lifestyle habits & repeat full liver panel on a shorter time horizon.
INCIDENTAL IMAGING FINDING SUGGESTIVE OF FATTY LIVER

Normal

Increased hepatic echogenicity
INCIDENTAL IMAGING FINDING SUGGESTIVE OF FATTY LIVER

• No pediatric data to guide decision-making
FOLLOW-UP OF INCIDENTAL IMAGING FINDINGS

Incidental imaging finding suggestive of hepatic steatosis

- Signs/symptoms of liver disease are present, OR liver biochemistry is abnormal
  - Further testing for causes of chronic liver disease, or referral

- No signs/symptoms of liver disease AND liver biochemistry is normal
  - Is the patient obese or overweight?
    - YES
      - Counsel on healthy lifestyle habits; follow liver indices and assess for RFs serially
    - NO
      - Assess for causes of secondary steatosis; consider referral
Treatment of NAFLD
NAFLD TREATMENT ENDPOINTS

• Gold standard: regression of NAFLD (e.g. steatosis, inflammation, and/or fibrosis)

• Silver: resolution of NASH (i.e. inflammation)

• Bronze: “sustained ALT decrease from baseline, particularly if durable (i.e. > 1 year) is a reasonable surrogate for response to treatment”

Vos et al, JPGN, 2016
THERAPEUTIC CHALLENGES

• No FDA-approved therapies for NAFLD

• With 2 notable exceptions, pediatric NAFLD trials have been small, unblinded, non-randomized, of short duration...

• Weight reduction is highly effective, but practically, very difficult to achieve and sustain
173 participants age 8-17 yrs with bx-confirmed NAFLD
800 IU vitamin E vs. 1000 mg metformin vs. placebo over 96 weeks
Primary outcome: ALT ≤ 50% baseline b/t weeks 48-96
Secondary outcome: liver histology
TONIC RESULTS

• Primary outcome:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vitamin E</th>
<th>Metformin</th>
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<tbody>
<tr>
<td>Sustained reduction ALT</td>
<td>17%</td>
<td>26%</td>
<td>16%</td>
</tr>
<tr>
<td>Mean ALT change from baseline</td>
<td>-35.2 U/L</td>
<td>-48.3 U/L</td>
<td>-41.7 U/L</td>
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• Secondary outcomes:

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<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vitamin E</th>
<th>Metformin</th>
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</thead>
<tbody>
<tr>
<td>Hepatocyte ballooning</td>
<td>0.1</td>
<td>-0.5*</td>
<td>-0.3*</td>
</tr>
<tr>
<td>NAS score</td>
<td>-0.7</td>
<td>-1.8*</td>
<td>-1.1</td>
</tr>
<tr>
<td>Resolution of NASH</td>
<td>28%</td>
<td>58%*</td>
<td>41%</td>
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In Children With Nonalcoholic Fatty Liver Disease, Cysteamine Bitartrate Delayed Release Improves Liver Enzymes but Does Not Reduce Disease Activity Scores

- 169 participants age 8-17 yrs with bx-confirmed NAFLD
- Cysteamine bitartrate (CB) vs. placebo over 52 weeks
- Primary outcome: liver histology
- Secondary outcome: change in ALT from baseline

Schwimmer et al, on behalf of the NASH CRN, *Gastroenterology*, December 2016
CYNCH RESULTS

• Primary outcome:

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<tr>
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<th>Placebo</th>
<th>CB</th>
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<tr>
<td>Improved histology at 52 weeks (decreased NAS score and no worsening of fibrosis)</td>
<td>28%</td>
<td>22%</td>
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• Secondary outcomes:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>CB</th>
</tr>
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<tbody>
<tr>
<td>Mean reduction in ALT from baseline</td>
<td>-8 U/L</td>
<td>-53 U/L*</td>
</tr>
<tr>
<td>Reduction in lobular inflammation</td>
<td>21%</td>
<td>36%*</td>
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“No currently available medications or supplements are recommended to treat NAFLD, because none have been proven to benefit the majority of NAFLD patients.”
WHAT DOES WORK: WEIGHT LOSS

- Steatosis: Weight loss ~3%
- Ballooning/Inflammation: Weight loss ≥5%
- NASH resolution: Weight loss ≥7%
- Fibrosis: Weight loss ≥10%

Adapted from Stephen Harrison, AASLD 2015
• Lifestyle modification to improve diet & increase physical activity are the 1st line therapy for all children with NAFLD

• Avoidance of sugar-sweetened beverages is suggested as a strategy to decrease adiposity

• Increasing moderate to high intensity physical activity and limiting screen time to < 2 hours/day is recommended for all children, including those with NAFLD
OUR APPROACH

- Involve RD early and often
- Sugary drink elimination is the first goal
- Provide specific, written (or illustrated) instructions, for diet & exercise
- Utilize local resources
  - YMCA, insurance, hospitals, rec centers
OUR APPROACH

• Set an achievable initial goal for weight reduction

• Program regular face time/accountability checks
  • Doesn’t necessarily have to be an MD/NP/PA

• Elicit family support/partnership
REMEMBER TO SET A GOOD EXAMPLE!
GOOD NEWS AHEAD...

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<tr>
<th>Agent</th>
<th>Mechanism</th>
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<tr>
<td>GFT-505</td>
<td>PPAR agonist</td>
</tr>
<tr>
<td>OCA</td>
<td>FXR agonist</td>
</tr>
<tr>
<td>Cenicriviroc</td>
<td>CCR2/CCL5 antagonist</td>
</tr>
<tr>
<td>Simtizumab</td>
<td>LOXL2 antagonist</td>
</tr>
<tr>
<td>Bovine colostrum</td>
<td>T-reg induction</td>
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<tr>
<td>Emriscasan</td>
<td>Caspase inhibitor</td>
</tr>
<tr>
<td>Aramchol</td>
<td>Synthetic fatty acid</td>
</tr>
<tr>
<td>GR-MD-02</td>
<td>Galectin-3 inhibitor</td>
</tr>
<tr>
<td>BMS986036</td>
<td>Recombinant FGF-21</td>
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Adapted from Stephen Harrison, AASLD 2015
**KEY REFERENCES**


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